Afferent arteriolar vasodilator effect of adenosine predominantly involves adenosine A2B receptor activation

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Feng MG, Navar LG. Afferent arteriolar vasodilator effect of adenosine predominantly involves adenosine A2B receptor activation. Am J Physiol Renal Physiol 299: F310–F315, 2010. First published May 12, 2010; doi:10.1152/ajprenal.00149.2010.—Adenosine is an important paracrine agent regulating renal vascular tone via adenosine A1 and A2 receptors. While A2B receptor message and protein have been localized to preglomerular vessels, functional evidence on the role of A2B receptors in mediating the vasodilatory action of adenosine on afferent arterioles is not available. The present study determined the role of A2B receptors in mediating the afferent arteriolar dilation and compared the effects of A2B and A2A receptor blockade on afferent arterioles. We used the rat in vitro blood-perfused juxtamedullary nephron technique combined with videomicroscopy. Single afferent arterioles of Sprague-Dawley rats were visualized and superfused with solutions containing adenosine or adenosine A2 receptor agonist (CV-1808) along with adenosine A2B and A2A receptor blockers. Adenosine (10 μmol/l) caused modest constriction and subsequent superfusion with SCH-58261 (SCH), an A2A receptor blocker, at concentrations up 10 μmol/l elicited only slight additional decreases in afferent arteriolar diameter with maximum effect at a concentration of 1 μmol/l (−11.0 ± 2.5%, n = 6, P < 0.05). However, superfusion of adenosine-treated vessels with MRS-1754 (MRS), an A2B receptor blocker, elicited greater decreases in afferent arteriolar diameter (−26.0 ± 4.7%, n = 5, P < 0.01). SCH did not significantly augment the adenosine-mediated afferent constriction elicited by MRS; however, adding MRS after SCH caused further significant vasoconstriction. Superfusion with CV-1808 dilated afferent arterioles (17.2 ± 2.4%, n = 6, P < 0.01). This effect was markedly attenuated by MRS (−22.6 ± 2.0%, n = 5, P < 0.01) but only slightly reduced by SCH (−9.0 ± 1.1%, n = 5, P < 0.05) and completely prevented by adding MRS after SCH (−24.7 ± 1.8%, n = 5, P < 0.01). These results indicate that, while both A2A and A2B receptors are functionally expressed in juxtamedullary arterioles, the powerful vasodilating action of adenosine predominantly involves A2B receptor activation, which counteracts A1 receptor-mediated vasoconstriction.

adenosine receptor antagonists; renal microcirculation; vascular biology; afferent arterioles; kidney

ADENOSINE IS AN ENDOGENOUS purine nucleoside derived from the degradation of ATP/AMP and serves as a paracrine agent influencing many physiological processes. Four subtypes of adenosine receptors have been identified: A1, A2A, A2B, and A3; all are guanine nucleotide-binding protein (G)-coupled receptors (6, 15, 25, 26, 28, 29), which are characterized by their capacity to either increase or decrease intracellular cAMP levels (13). A2A and A2B receptors are coupled to G3 protein signaling and mediate biological effects opposite to A1 and A3 receptors, which are coupled to G1 protein signaling (13). All four subtypes of adenosine receptors are commonly expressed in vascular smooth muscle cells. Both adenosine A1 and A2 receptors are expressed in the rat kidney in both vascular and tubular cells (1, 21, 24, 44, 48). In particular, preglomerular microvessels have abundant expression of A1 and A2 receptors (21). Molecular studies have shown that A2B is the predominant A2 receptor that is expressed in preglomerular arterioles (21); however, there are no functional studies demonstrating the actions of A2B receptor activation or blockade on preglomerular microvessels.

Although adenosine primarily elicits vasodilation via A2 receptors in many tissues, in the renal vasculature, adenosine elicits biphasic effects with vasoconstriction via A1 receptors and vasodilation via A2 receptors. As the concentration of adenosine increases, the vasodilatory stimulus becomes predominant (10, 18, 27, 35, 36, 38, 41). Activation of adenosine A1 receptors in the renal vasculature results in vasoconstriction that reduces the glomerular filtration rate (30, 32) and renal blood flow (4), enhances tubuloglomerular feedback responses (37), and inhibits renin secretion (38). Adenosine has been suggested as both a mediator and a modulator of renal autoregulation and the tubuloglomerular feedback response (10, 19, 26, 42). However, activation of A2 receptors abrogates the counteracting influences of A1 receptor activation, leading to marked vasodilation and decreased afferent arteriolar autoregulatory efficiency (3, 10, 37). A2 receptor-mediated vasoconstriction results from stimulation of Gs, leading to increased cAMP that is partially mediated via epoxyeicosatrienoic acid (EETs) release (7). Cytochrome P-450 epoxygenase metabolites alter vascular tone in afferent arterioles and modify the autoregulatory efficiency of the preglomerular microcirculation (8, 20). Activation of A2 receptor stimulates EETs in preglomerular microvessels, suggesting that it may affect the following major indexes of renal function: renal vascular resistance, glomerular filtration rate, renal interstitial pressure, and medullary blood flow (8). Adenosine also dilates efferent arterioles at concentrations compatible with activation of the A2B receptor subtype (1). In the renal vasculature, low-dose adenosine evokes vasoconstriction via A1 receptor, and this effect is opposed by vasodilatory signals via A2 receptor (10). However, it has not been determined whether the opposing effect is mediated by A2A or A2B receptors. In the present study, we used the rat in vitro blood-perfused juxtamedullary nephron technique combined with videomicroscopy; adenosine and an adenosine A2 receptor agonist; a selective, high-affinity adenosine A2B receptor blocker; and a selective A2A receptor blocker to determine the role of A2B receptors in opposing the afferent arteriolar vasoconstrictor response to adenosine and compared the effects of A2B and A2A receptor blockade on afferent arterioles.
MATERIALS AND METHODS

The experimental protocols and procedures were approved by the Tulane University Institutional Animal Care and Use Committee.

Videomicroscopic measurements of afferent arteriolar diameters were performed using the isolated blood-perfused juxtamedullary nephron preparation, as previously described (10, 11, 12). Briefly, each experiment used one male Sprague-Dawley rat (Charles River Laboratories, Wilmington, MA), weighing 370–410 g, serving as blood and kidney donor. Rats were anesthetized with pentobarbital sodium (50 mg/kg ip), and a cannula was inserted in the left carotid artery for blood collection. Blood was collected in a heparinized (500 units) syringe via the carotid arterial cannula and centrifuged to separate the plasma and cellular fractions. The buffy coat was removed and discarded. After sequential passage of the plasma through 5- and 0.22-μm filters (Gelman Sciences, Ann Arbor, MI), erythrocytes were added to achieve a hematocrit of 33%. This reconstituted blood was passed through a 5-μm nylon mesh and thereafter stirred continuously in a closed reservoir that was pressurized with a 95% O2-5% CO2 gas mixture.

The right kidney was perfused through a cannula inserted in the superior mesenteric artery and advanced to the right renal artery. The initial perfusate was a Tyrode’s solution (pH 7.4) containing 5.1% BSA and a mixture of L-amino acids thereafter stirred continuously in a closed reservoir that was pressurized with a 95% O2-5% CO2 gas mixture. The kidney was excised and sectioned longitudinally, retaining the papilla intact with the perfused dorsal two-thirds of the organ. The papilla was reflected to expose the pelvic mucosa and tissue covering the inner cortical surface. Overlying tissue was removed to expose the tubules, glomeruli, and related vasculature of the juxtamedullary nephrons. The arterial supply of the exposed microvasculature was isolated by ligating the larger branches of the renal artery.

After the dissection was complete, the Tyrode’s perfusate was replaced with the reconstituted blood. Perfusion pressure was monitored by a pressure catheter centered in the tip of the perfusion cannula. Renal perfusion pressure was regulated by adjusting the rate of gas inflow into the blood reservoir and set at 100 mmHg. The inner cortical surface of the kidney was continuously superfused with a warmed (37°C) Tyrode’s solution containing 1% albumin. The tissue was transilluminated on the fixed stage of a microscope (Nikon equipped with a water-immersion objective (×40). Video images of the microvessels were transferred by a Newvicon camera (model NC-67M; Dage-MTI, Michigan City, IN) through an image enhancer (model MFJ-1452; MFJ Enterprises, Starkville, MS) to a video monitor (Conrac Display Systems, Covina, CA). The video signal was recorded on videotape for later analysis. Afferent arteriolar inside diameters were measured at 30-s intervals using a calibrated digital image-acquiring monitor (Instrumentation for Physiology and Medicine, San Diego, CA). Treatments were administered by superfusing the tissue with a Tyrode’s solution containing the agent to be tested or the vehicle solution. The following agents were used in this study: adenosine and an adenosine A2 receptor agonist, 2-phenylaminoadenosine (CV-1808) (38); a selective, high-affinity adenosine A2B receptor blocker, 8-[4-[(4-cyanophenyl) carbamoylmethyl]oxy]phenyl]-1,3-di(n-propyl)xanthine hydrate [MRS-1754 (MRS)] (22, 23); and a selective A2A receptor blocker, 7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine [SCH-58261 (SCH)] (2, 46, 47). All agents were purchased from Sigma (St. Louis, MO).

Experimental protocols. For each experiment, a single afferent arteriole from one rat that showed adequate blood flow was selected for study. After a 15- to 20-min equilibration period, an experimental protocol was initiated consisting of consecutive 10- to 30-min treatment periods. Steady-state diameter determinations were calculated from the average of measurements obtained during the final 5 min of each treatment period at a renal arterial pressure of 100 mmHg.

The first series of experiments was performed to determine the dose-response relationships for the adenosine A2A receptor blocker SCH and the adenosine A2B receptor blocker MRS on adenosine-treated afferent arteriolar diameters and to find their most effective concentrations. Afferent arteriolar inside diameters were measured during sequential exposure of the vessel to superfusate solutions containing 10 μM adenosine followed by: 1a) control vehicle and 1b) SCH at concentrations of 0.001, 0.01, 0.1, 1, 10, and 100 μmol/l; or 2a) control vehicle and 2b) MRS at concentrations of 0.001, 0.01, 0.1, 1, 10, and 100 μmol/l. The dose of adenosine used was determined from preliminary experiment as one that would elicit sustained partial vasconstrictor responses without eliciting biphasic effects.

A second series of experiments was performed to determine the effects of MRS and SCH combined treatment on adenosine-treated afferent arteriolar diameters. Afferent arteriolar inside diameters were measured during sequential exposure of the vessel to superfusate solutions containing 10 μmol/l adenosine followed by either first adding MRS (1 μmol/l) then SCH (1 μmol/l) or first adding SCH (10 μmol/l) then MRS (1 μmol/l).

A third experimental protocol was performed to determine the effects of CV-1808 on resting afferent arteriolar diameters. Afferent arteriolar inside diameters were measured during sequential exposure of the vessel to superfusate solutions containing CV-1808 at concentrations of 0.002, 0.02, 0.2, and 2 μmol/l.

A forth series of experiments was performed to determine the effects of MRS and SCH combined treatment on CV-1808-treated afferent arteriolar diameters. Afferent arteriolar inside diameters were measured during sequential exposure of the vessel to superfusate solutions containing CV-1808 (2 μmol/l) followed by either first adding MRS (1 μmol/l) then SCH (1 μmol/l) or first adding SCH (1 μmol/l) then MRS (1 μmol/l).

Statistical analysis. All data are reported as means ± SE. Data were analyzed by two-way ANOVA or one-way ANOVA, followed by a Bonferroni’s Multiple-Comparison post hoc test. Values of P < 0.05 were considered statistically significant.

RESULTS

Effects of MRS and SCH on adenosine-treated afferent arteriolar diameters. Continuous superfusion with the lower dose of adenosine (10 μM) caused a modest but sustained vasoconstriction of afferent arterioles (−10.2 ± 1.0%, n = 9, P < 0.01). The maximum changes in diameters were reached at 30–90 s. As shown in Fig. 1, in the presence of adenosine (10 μmol/l), superfusion with SCH, an A2A receptor blocker, at concentrations of 0.001, 0.01, 0.1, 1, and 10 μmol/l elicited only slight further decreases in afferent arteriolar diameter from 16.0 ± 0.3 to 15.3 ± 0.4, 15.0 ± 0.3, 14.1 ± 0.3, and 14.5 ± 0.3 μm, with maximum effect at a concentration of 1 μmol/l, −1.10 ± 2.5% (Fig. 1A, n = 6, P < 0.05). However, superfusion of adenosine-treated vessels with MRS, an A2B receptor blocker, at concentrations of 0.001, 0.01, 0.1, and 1 μmol/l caused greater decreases in afferent arteriolar diameter from 15.7 ± 0.5 to 14.8 ± 0.6, 12.9 ± 0.5, and 12.3 ± 0.4 μm, with a maximum decrease of −26.0 ± 4.7% (Fig. 1B, n = 5, P < 0.01). These results indicate that even relatively low concentrations of adenosine activate A2B vasodilator responses, which mitigate the A1-mediated vasoconstriction. Effects of MRS and SCH combined treatment on adenosine-treated afferent arteriolar diameters. The addition of SCH or MRS elicited further changes in afferent arteriolar diameters with new steady-state diameters. As shown in Fig. 2, adding 1 μmol/l SCH did not significantly augment the adenosine-mediated afferent constriction elicited by 1 μmol/l MRS with...
changes in adenosine-treated afferent arteriolar diameter (A, n = 6, P < 0.01); however, superfusion with MRS elicited greater decreases on adenosine-treated afferent arteriolar diameter (B, n = 5, P < 0.01). Values are means ± SE. *P < 0.01 vs. control condition at renal perfusion pressure of 100 mmHg.

Effects of CV-1808 on afferent arteriolar diameters. Figure 3 shows the effects of CV-1808 on resting afferent arteriolar diameters. In response to superfusion with CV, an adenosine A2 receptor agonist, at concentrations of 0.002, 0.02, 0.2, and 2 μmol/l, afferent arteriolar diameter increased from 17.0 ± 0.3 to 17.2 ± 0.4, 17.8 ± 0.4, 18.5 ± 0.5, and 19.9 ± 0.7 μm, 17.2 ± 2.4% (n = 6, P < 0.01).

Effects of MRS and SCH combined treatment on CV-1808-treated afferent arteriolar diameters. As shown in Fig. 4, in the presence of CV-1808 (2 μmol/l), superfusion with 1 μM SCH decreased afferent arteriolar diameter slightly from 19.9 ± 0.7 to 18.1 ± 0.6 μm, −9.0 ± 1.1%; however, subsequent superfusion with MRS after SCH at 1 μmol/l decreased afferent arteriolar diameter to a greater extent from 18.1 ± 0.6 to 15.1 ± 1.2 μm, −24.7 ± 1.8% (Fig. 4A, n = 5, P < 0.01). In the presence of CV-1808 (2 μmol/l), initial superfusion with MRS at concentrations of 1 μmol/l decreased afferent arteriolar diameter significantly from 20.0 ± 0.6 to 15.4 ± 0.7 μm, −22.6 ± 2.0% (n = 5, P < 0.01). Subsequent superfusion with SCH after MRS did not cause further significant decreases in afferent arteriolar diameter from 15.4 ± 0.7 to 14.7 ± 0.8 μm, −4.9 ± 1.3% (Fig. 4B, n = 5, P > 0.05 via MRS group).

DISCUSSION

This study demonstrates that adenosine mediates vasodilation of renal afferent arterioles predominantly via A2B receptors. Unlike the vasculature of most tissues and organs in which A1 receptors are not widely expressed, both A1 and A2 receptors are abundant in the renal microvasculature, which makes delineation of the renal vascular actions of adenosine comparatively difficult; thus, the composite renal vascular actions of adenosine are complex and not fully appreciated. It is recognized that interactions between adenosine A1 and A2 receptors are abundant in the renal microvasculature, which makes delineation of the renal vascular actions of adenosine comparatively difficult; thus, the composite renal vascular actions of adenosine are complex and not fully appreciated.
receptors play important modulatory roles in regulating renal afferent arteriolar tone, and activation of A2 receptors offsets the counteracting influence of A1 receptors resulting in vasodilation (10, 18, 27, 35, 36, 38, 41). However, previous studies regarding the function of the A2 receptors have been focused primarily on A2A subtype, with the effects of A2B receptors given less attention. Most of these studies suggested that the vasodilator effect of adenosine mainly involves adenosine A2A receptor activation rather than A2B receptor activation (17, 42, 43). Some results were based on using 3,7-dimethyl-1-propargylxanthine (DMPX) as a receptor blocker (9, 34, 39). However, DMPX is a nonspecific adenosine receptor blocker that blocks both A2A and A2B receptors. Thus the conclusions reached in previous studies are not consistent with our findings because these studies did not use selective A2A and A2B receptor blockers. The results reported by Jackson et al. (21) that A2B receptor is the predominant A2 receptor expressed in preglomerular afferent arteriolar smooth muscle cells prompted us to reevaluate this question using highly selective A2B and A2A receptor blockers.

In the present study, we found that superfusion with a low concentration of adenosine (10 μmol/l) caused a partial constriction of juxtamedullary afferent arterioles, which then allowed us to determine if adenosine-induced vasoconstriction could be enhanced by the A2A and A2B receptor antagonists (SCH and MRS). The present results are consistent with previous studies in our laboratory showing that adenosine at low concentration causes modest constriction of juxtamedullary afferent arterioles, which was markedly enhanced by the A2 receptor antagonist (DMPX) (10, 27). These data indicate that, while A1 receptors are more sensitive to adenosine than A2 receptors, even a relatively low dose of adenosine also activates A2 receptors. Adenosine binds with very high affinity to the A1 receptor in its high-affinity conformation (16, 31, 33); however, the A2B receptor is a lower-affinity receptor that may only partially oppose the A1-mediated vasoconstriction under physiological conditions and only become dominant with increased extracellular adenosine levels (5, 14). Adenosine exerts its biological effects through binding to the G protein-coupled adenosine receptors. Activation of A1 receptors inhibits adenylyl cyclase (AC) and cAMP activity in vascular smooth muscles. Conversely, activation of A2A and A2B receptors stimulates AC and cAMP activity in vascular smooth muscles. A1 receptors also activate phospholipase C and phospholipase D, and A2B receptors can also stimulate phospholipase C via Gq activation (3, 13, 28, 37, 42). Thus, during superfusion with adenosine, both A1 and A2 receptors were activated to produce opposing effects; at the low concentrations, adenosine predominantly activates A1 receptors, leading to vasoconstriction, and A2 receptor blockade enhances vasoconstriction in afferent arterioles.

![Graph](http://ajprenal.physiology.org/)

Fig. 3. Effects of CV-1808 on afferent arteriolar diameters. CV-1808 cause significant increases in afferent arteriolar diameter (n = 6, P < 0.01). Values are means ± SE. *P < 0.05 and **P < 0.01 vs. control condition at renal perfusion pressure of 100 mmHg.

![Graph](http://ajprenal.physiology.org/)

Fig. 4. Effects of MRS and SCH combined treatment on CV-1808-treated afferent arteriolar diameters. In the presence of CV-1808 (2 μmol/l), superfusion with SCH (1 μmol/l) decreased afferent arteriolar diameter slightly (A, n = 5, P > 0.05). However, superfusion with MRS after SCH (1 μmol/l) caused further significant decreases in afferent arteriolar diameter (B, n = 5, P < 0.01). Changes in diameter are expressed as μm (A and B) or as a percentage (C). Values are means ± SE. **P < 0.01 vs. control treatment at renal perfusion pressure of 100 mmHg.
The present data also evaluated the specific role of adenosine $A_{2A}$ and $A_{2B}$ receptors by using the highly selective $A_{2A}$ and $A_{2B}$ receptor blockers SCH (22, 23) and MRS (2, 46, 47). To find the most effective concentration of SCH and MRS, we determined the dose-response relationships for SCH and MRS on adenosine-mediated vasoconstriction. We found that, in the presence of adenosine (10 μmol/l), superfusion with SCH, an $A_{2A}$ receptor blocker, elicited only slight additional decreases in afferent arteriolar diameter with maximum effect at a concentration of 1 μmol/l. In contrast, superfusion of adenosine-treated vessels with MRS, an $A_{2B}$ receptor blocker, caused greater decreases in afferent arteriolar diameter. Adding 1 μmol/l SCH did not significantly augment the adenosine-mediated afferent constriction elicited by MRS; however, adding MRS after SCH caused further significant vasoconstriction, indicating that most of the vasodilating effect was due to activation of $A_{2B}$ receptor. We certainly acknowledge the issue related to the nonselective actions of putative adenosine blockers. However, MRS is a highly potent and selective adenosine $A_{2B}$ receptor blocker that is 254-fold more selective for human $A_{2B}$ receptors than human $A_{2A}$ receptors (22, 23). SCH is the most potent antagonist of the human adenosine $A_{2A}$ receptor blocker (2, 46, 47). Importantly, significant augmentation of adenosine-mediated vasoconstriction was observed even at MRS concentration of 10 nM, which would not be expected to have any effect on $A_{2A}$ receptor. SCH elicited only slight decreases in afferent arteriolar diameter, and the most effective concentration of SCH is $\sim 1 \mu M$. As the concentration of SCH increased, the vasoconstriction stimulus became less, which may be due to the higher dose partially blocking $A_1$ receptors. Because $A_{2A}$ receptors should be fully blocked by SCH at 1 μM, it is not likely that the additional significant vasoconstriction caused by adding MRS after SCH is due to $A_{2A}$ receptor blockade rather than $A_{2B}$ receptor blockade. Furthermore, 1 μM SCH or adding 1 μM SCH after MRS elicited only slight decreases in afferent arteriolar diameter, which would be related to $A_{2A}$ receptor blockade. Blocking $A_1$ receptors would be expected to cause vasodilation, not vasoconstriction, making it unlikely that the vasoconstriction of afferent arterioles is associated with blockade of $A_1$ receptors.

In further studies, we found that, in the presence of CV-1808, an adenosine $A_2$ receptor agonist, superfusion with SCH decreased afferent arteriolar diameter only slightly; however, superfusion with MRS after SCH decreased afferent arteriolar diameter markedly. In the presence of CV-1808, superfusion with MRS decreased afferent arteriolar diameter back to control levels, and superfusion with SCH after MRS did not cause further significant decreases in afferent arteriolar diameter. These data show that, while both $A_{2B}$ and $A_{2A}$ receptors are functionally expressed in juxtamedullary afferent arterioles, the opposing vasodiator effect during adenosine-mediated afferent arteriolar vasoconstriction is predominantly via activation of $A_{2B}$ receptors. These results provide functional support to the molecular studies demonstrating abundant expression of $A_1$ and $A_{2B}$ but not $A_{2A}$ or $A_3$ receptor protein and mRNA in renal preglomerular microvascular tissue, indicating that $A_{2B}$ receptor is the predominant $A_2$ receptor in afferent arterioles (21, 45).

In summary, adenosine at low concentration constricted afferent arterioles. SCH, an $A_{2A}$ receptor blocker, elicited only slight additional decreases in both adenosine and CV-1808-treated afferent arteriolar diameter. However, MRS, an $A_{2B}$ receptor blocker, elicited greater decreases in both adenosine and CV-1808-treated afferent arteriolar diameters. Adding SCH did not significantly augment the adenosine-mediated afferent constriction elicited by MRS; however, adding MRS after SCH caused further significant vasoconstriction. Superfusion with CV-1808, an $A_2$ agonist, increased afferent arteriolar diameter, which was decreased by SCH slightly and by MRS markedly. Superfusion with MRS after SCH caused further significant decreases in afferent arteriolar diameter. However, superfusion with SCH after MRS did not cause further significant decreases in CV-1808-treated afferent arteriolar diameter. These results demonstrate that the powerful vasodilating action of adenosine $A_2$ receptors counteracts $A_1$ receptor-mediated vasoconstriction and indicate that, while both $A_{2A}$ and $A_{2B}$ receptors are functionally expressed in juxtamedullary afferent arterioles, the vasodilator effect of adenosine predominantly involves $A_{2B}$ receptor activation.

**Perspectives**

Adenosine is an important paracrine agent regulating renal vascular tone via adenosine $A_1$ and $A_2$ receptors. The opposing vasodilator effects between adenosine $A_1$ and $A_2$ ($A_{2A}$, $A_{2B}$) receptors are complex and not fully understood. The present results demonstrate the substantial importance of $A_{2B}$ Receptors in mediating renal preglomerular arteriolar dilatation; activation of $A_{2B}$ receptors is primarily responsible for the vasodilator effect of adenosine. Because $A_{2A}$ are not abundantly expressed in renal preglomerular microvascular tissue, $A_{2B}$ may be particularly significant in mediating afferent arteriolar vasodilation. Furthermore, it is likely that, when $A_1$ receptors are pharmacologically blocked or genetically deleted, the $A_{2B}$ receptors exert a powerful vasodilator effect that may block mechanisms regulating afferent arterioles.

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**DISCLOSURES**

No conflicts of interest are declared by the authors.

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